STATISTICAL ANALYSIS PLAN

A Phase 3, Multicenter, Randomized, Double–Masked and Placebo–Controlled Study Evaluating the Efficacy and Safety of Tanfanercept Ophthalmic Solution 0.25% Compared to Placebo in Subjects with Dry Eye

Sponsor: HanAll Biopharma Co., Ltd.

Protocol Number: HL036-DED-US-P302

Author: [redacted]

Statistics & Data Corporation

Date: 07-FEB-2022

Version: 0.1

A Phase 3, Multicenter, Randomized, Double–Masked and Placebo–Controlled Study Evaluating the Efficacy and Safety of Tanfanercept Ophthalmic Solution 0.25% Compared to Placebo in Subjects with Dry Eye

Protocol Number: **HL036-DED-US-P302**

Version: **1.0**

Date: **23-JAN-2023**

Statistical Analysis Plan Approval
Veristat, Inc.

Prepared/Updated by	Job Title
DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I am the author of this document Signing Time: 23-Jan-2023 | 2:59:49 PM EST EE88EE850D974568AD83AA0AEE1AEA3B	[redacted]

Reviewed by	Job Title
DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I have reviewed this document Signing Time: 24-Jan-2023 | 12:10:30 PM EST 852EF035F1A049D0A0B9BC5A9E7D5C0C	[redacted]

Sponsor Approval

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate and are consistent with the statistical methodology described in the related study protocols, clinical development plan, and all applicable regulatory guidances and guidelines.
I have discussed any questions I have regarding the contents of this document with the biostatistical author.
I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments.

Sponsor Signatory

Approved by	Job Title
DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 23-Jan-2023 | 7:48:13 PM EST A2DE17C2A04144F2A2CB6EE2AA22005D	[redacted]

Table of Contents

List of Abbreviations

Abbreviation	Definition
ADA	Anti-Drug Antibodies
AE	Adverse Event
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
BCVA	Best-Corrected Visual Acuity
BID	*Bis in die* (Twice Daily)
CCSS	Central Corneal Staining Score
CFB	Change from Baseline
CI	Confidence Interval
CS	Clinically Significant
eCRF	Electronic Case Report Form
EDS	Eye Dryness Score
ETDRS	Early Treatment of Diabetic Retinopathy Study
ICH	International Conference on Harmonisation
IOP	Intraocular Pressure
IP	Investigational Product
IRT	Interactive Response Technology
ITT	Intent-to-Treat
LOCF	Last Observation Carried Forward
logMAR	Logarithm of the Minimum Angle of Resolution
LS	Least Squares
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model repeated measures
NCS	Not Clinically Significant
OD	*Oculus dexter* (Right Eye)
OS	*Oculus sinister* (Left Eye)
OSDI©	Ocular Surface Disease Index©
PDF	Portable Document Format
PMM	Pattern-Mixture Model
PP	Per Protocol
PT	Preferred Term
RTF	Rich Text Format
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDC	Statistics & Data Corporation
SE	Standard Error
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event

Abbreviation	Definition
TE-SAE	Treatment-Emergent Serious Adverse Event
TFBUT	Tear Film Break-Up Time
VA	Visual Acuity
VAS	Visual Analog Scale
WHODrug	World Health Organization Drug Dictionary

1. Introduction

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and reporting for protocol HL036-DED-US-P302 Version 4.0, dated 22-JUN-2022

This SAP is being written with due consideration of the recommendations outlined in the most recent International Conference on Harmonisation (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials, E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials, and the most recent ICH E3 Guideline entitled Guidance for Industry: Structure and Content of Clinical Study Reports.

This SAP describes the data that will be analyzed and the subject characteristics, efficacy, and safety assessments that will be evaluated. This SAP provides details of the specific statistical methods that will be used. The statistical analysis methods presented in this document will supersede the statistical analysis methods described in the clinical protocol. If additional analyses are required to supplement the planned analyses described in this SAP they may be completed and will be identified in the clinical study report.

2. Study Objectives

The objective of this study is to compare the safety and efficacy of Tanfanercept Ophthalmic Solution 0.25% to placebo for the treatment of the signs and symptoms of dry eye.

2.1 Primary Variables

The primary efficacy variables of the study are:

- Central corneal staining score (CCSS; sign), mean change from baseline (V2) to Day 57 ± 3 (V6, Week 8)
- Eye dryness score on Visual Analog Scale (EDS-VAS; symptom), mean change from baseline (V2) to Day 57 ± 3 (V6, Week 8)

2.2 Secondary Variables

The secondary efficacy variables include the following:

- Fluorescein staining (Ora Calibra® scale) by region: central, superior, inferior, temporal, nasal, corneal sum, conjunctival sum, and total staining
- Conjunctival lissamine green staining (Ora Calibra® scale) by region: central, superior, inferior, temporal, nasal, corneal sum, conjunctival sum, and total staining
- Conjunctival redness
- Unanesthetized Schirmer's Test
- Tear film break-up time (TFBUT)
- Visual Analog Scale (VAS) (reported symptoms include burning/stinging, itching, foreign body sensation, blurred vesion, eye dryness, photophobia, and pain)
- Ocular Surface Disease Index© (OSDI©)

- Ora Calibra® Ocular Discomfort Scale
- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire

2.3 Safety Variables

The safety variables include the following:

- Adverse event (AE) query
- Visual acuity (VA)
- Slit-lamp evaluation
- Intraocular Pressure (IOP)
- Dilated fundoscopy
- Immunogenicity to Tanfanercept Ophthalmic Solution 0.25% in serum

2.4 Other Variables

The other variables include the following:

- Ora Calibra® Drop Comfort Scale
- Ora Calibra® Drop Comfort Questionnaire

2.5 Statistical Hypotheses

The statistical hypotheses are stated in terms of two-sided hypotheses, although statistical inference will be one-sided, with the direction of interest in the differences in treatment group means as stated in Section 13.1. The primary endpoints will be tested in a hierarchical fixed sequence in the following order.

H_{01}: There is no difference between Tanfanercept Ophthalmic Solution 0.25% and placebo in the change from baseline (Visit 2 [Day 1]) of the CCSS at Day 57 ± 3 (Visit 6, Week 8) in the ITT Population, using the Ora Calibra® scale (Ex. H_{01}: $\mu_t = \mu_p$).

H_{A1}: The change from baseline (Visit 2 [Day 1]) of the CCSS at Day 57 ± 3 (Visit 6, Week 8) using the Ora Calibra® scale is not equal with Tanfanercept Ophthalmic Solution 0.25% than with placebo in the ITT Population (Ex. H_{A1}: $\mu_t \neq \mu_p$).

H_{02}: There is no difference between Tanfanercept Ophthalmic Solution 0.25% and placebo in the change from baseline (Visit 2 [Day 1] of the EDS on VAS at Day 57 ± 3 (Visit 6, Week 8) in the ITT Population (Ex. H_{02}: $\mu_t = \mu_p$).

H_{A2}: The change from baseline (Visit 2 [Day 1]) of the EDS on VAS is not equal with Tanfanercept Ophthalmic Solution 0.25% than with placebo at Day 57 ± 3 (Visit 6, Week 8) in the ITT Population (Ex. H_{A2}: $\mu_t \neq \mu_p$).

2.6 Estimands

The primary analysis of the primary endpoints will use the Intent-to-Treat (ITT) population for the primary endpoints of Change from Baseline (CFB) of CCSS at Day 57 ± 3 and CFB of EDS-VAS at Day 57 ± 3, and the primary analysis will be executed using mixed model repeated measures (MMRM) with multiple imputation methodology using the following estimand:

Estimand 1:

- Population:
  - ITT population
- Endpoints:
  - CFB in CCSS in the study eye at Day 57 ± 3 in the ITT population
  - CFB in EDS from VAS at Day 57 ± 3 in the ITT population
- Intercurrent events:
  - Discontinuation of study medications is ignored. Measures obtained after discontinuation of study medication will be analyzed. [treatment policy strategy]
  - Non-optimal compliance is ignored. Measures will be analyzed regardless of treatment compliance. [treatment policy strategy]
  - Use of prohibited concomitant medications is ignored. Measures obtained after use of prohibited concomitant medications will be analyzed. [treatment policy strategy]
  - Withdrawal due to lack of efficacy or adverse events: Missing values assumed to be missing not at random will be multiply imputed using placebo group-based PMM imputation. [hypothetical strategy]
  - Missing data with withdrawal or withdrawal due to reasons other than lack of efficacy or adverse events: Missing values assumed to be missing at random will be multiply imputed using randomized treatment group-based MCMC imputation. [hypothetical strategy]
- Population-level summary:
  - Difference in the mean CFB in CCSS in the study eye at Day 57 ± 3 between Tanfanercept and placebo in the ITT population.
  - Difference in the mean CFB in EDS (VAS) at Day 57 ± 3 between Tanfanercept and placebo in the ITT population.

If the rate of missing data for EDS-VAS is imbalanced between treatment groups (demonstrated by Fisher's exact test with a p-value of <0.05) and the rate of missing data for EDS-VAS is ≥ 10% in all subjects, then the primary analyses will utilize the ITT population using the permutation test with trimmed means methodology, as detailed in Estimand 2.

Estimand 2:

- Population:
  - ITT population
- Endpoint:
  - CFB in CCSS in the study eye at Day 57 ± 3 in the ITT population
  - CFB in EDS from VAS at Day 57 ± 3 in the ITT population
- Intercurrent event:
  - Discontinuation of study medications is ignored. Measures obtained after discontinuation of study medication will be analyzed. [treatment policy strategy]
  - Non-optimal compliance is ignored. Measures will be analyzed regardless of treatment compliance. [treatment policy strategy]
  - Use of prohibited concomitant medications is ignored. Measures obtained after use of prohibited concomitant medications will be analyzed. [treatment policy strategy]
  - Withdrawal or missed assessments for any reason. Missing values will be removed, following the trimmed means methodology laid out in Permutt T, Li F. [hypothetical strategy]. The trimmed means strategy is as follows:
    - Using an analysis of covariance (ANCOVA), a linear model is fit to the data with treatment as factor and baseline value as covariate. The beta coefficient for treatment is discarded and only the Y (outcome) value, the beta coefficient for baseline score, and X (baseline score) are considered. $Y - \beta(X)$ is then calculated for each subject for the purpose of ranking.
    - Next, the proportions of subjects with missing values in the control and treatment arms are identified. The greater proportion of the two arms is then used as the percentile floor in which observations must be better. Those observations that are not better than the floor are trimmed (removed). Missing values are included in the calculation of the percentile floor value as values worse than the percentile.
    - After trimming is done, MMRM is used on the two analysis sets to find an observed treatment effect. The MMRM model will be based on the final model as described in Section 13.1.1.To determine the p-value and 95% CI, 10,000 permutations of the data will be run and the trimming methodology will be repeated. The number of permutation datasets that result in an effect size greater than the observed effect size divided by the number of permutations will be the p-value. The 95% CI will be calculated using the 2.5^{th} and 97.5^{th} percentiles of the permutation distribution.
- Population-level summary:
  - Difference in the mean CFB in EDS-VAS at Day 57 ± 3 between Tanfanercept and placebo in the ITT population.

3. Study Design and Procedures

3.1 General Study Design

This is a Phase 3, multicenter, randomized, prospective, double-masked, placebo-controlled, parallel-arm design. Subjects will be randomized to one of the following treatment arms at Visit 2 (Day 1) and will be instructed to follow a twice daily (BID) dosing regimen:

- Tanfanercept Ophthalmic Solution 0.25% (N~150)
- Placebo Ophthamlic Solution (N~150)

Approximately 300 subjects will be randomly assigned to one of two treatment groups (1:1) to receive either Tanfanercept Ophthalmic Solution 0.25% or Placebo Ophthalmic Solution as topical ophthalmic drops administered bilaterally twice daily (BID). The total number of expected participants, including screen failures, is approximately 857 subjects.

[redacted]

Information regarding subjects, Sponsor, Clinical Research Organizations, and site personnel will be masked and treatment group assignment will be unknown to subjects.

During the 14-day screening period, endpoint measurements will be taken to ascertain eligibility to enter the study. Those who qualify will be randomized to receive study drug in a double-masked fashion for 56 days. Subjects will self-administer drops BID.

Table 1 shows the scheduled study visits, planned study day (note that there is no Day 0 and that Day 1 corresponds to the day of randomization), the acceptable visit window for each study visit, and the analysis visit window.

Table 1. Scheduled Study Visits, Planned Study Days, and Visit Windows

Scheduled Visit	Planned Study Day	Visit Window	Analysis Visit Window
Visit 1	Day -14	± 2 days	Day -16 to Day -1
Visit 2	Day 1	N/A	N/A
Visit 3	Day 8	± 1 day	Day 2 to Day 11
Visit 4	Day 15	± 2 days	Day 12 to Day 21
Visit 5	Day 29	± 2 days	Day 22 to Day 43
Visit 6	Day 57	± 3 days	Day 44 to Day 60

Analysis visit windows will be implemented for efficacy analyses only. If a subject has multiple assessments/results reported within an analysis visit window, the following selection hierarchy will be implemented.

1. If results are reported at the planned study day and at an unscheduled visit, then the results reported on the planned study day will be selected.
2. If no results are reported on the planned study day, then the results/observation reported at the study day closest to the planned study day will be selected.

If there is a tie on the number of days prior to planned study day and post planned study day, then the results/observation reported prior to planned study day will be selected.

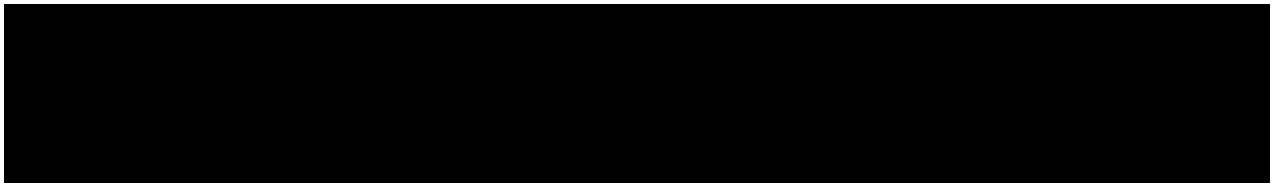
3.2 Schedule of Visits and Assessments

The schedule of visits and assessments is provided in Appendix 2.

4. Study Treatments

4.1 Method of Assigning Subjects to Treatment Groups

Prior to initiation of study run-in at Day -14, each subject who qualifies for entry will be assigned a screening number. All screening numbers will be assigned in strict numerical sequence at a site and no numbers will be skipped or omitted. If all inclusion criteria are met and none of the exclusion criteria are met at Day -14 and Day 1, each qualifying subject will then be assigned a randomization number (assigning them to Tanfanercept Ophthalmic Solution 0.25% or Placebo Ophthalmic Solution) at the end of Day 1 using the Interactive Response Technlogy (IRT). The randomization number will be recorded on the Subject's source document and the electronic Case Report Form (eCRF) .



The randomization number will be recorded on the Subject Record Page and eCRF. A new kit will be dispensed at Day 1, Day 15, and Day 29based on the subject's randomization. The Day 1 kit will be re-dispensed at Day 8. At Day 29, subjects will receive two assigned study drug kits with sufficient supply to last until Day 57. The Sponsor, investigators, and study staff will be masked during the randomization process and throughout the study.

4.2 Masking and Unmasking

All subjects, investigators, and study personnel involved with the conduct of the study will be masked with regard to treatment assignments. When medically necessary, the investigator may need to determine what treatment arm has been assigned to a subject. When possible (i.e., in non-emergent situations), Ora and/or the study sponsor should be notified before unmasking study drug. The unmasked subject will be discontinued from the study.

5. Sample Size and Power Considerations

The primary objective of the study is to demonstrate a statistically significant difference between the active treatment and placebo.

Per the protocol, this study was expected to randomize 150 subjects in each of the two treatment arms, for a total of 300 randomized subjects. Assuming a 10% drop out rate, 135 subjects per group are expected to complete the study.

Assuming a common standard deviation (SD) in the change from baseline (Day 1) to Day 57 for CCSS of [redacted] a sample size of 135 evaluable subjects per group will have 99.4% power to detect a difference of [redacted] between the active treatment group and the placebo group at a significance level of 0.05.

After randomizing 260 subjects, the Sponsor conducted a masked interim assessment of the sample size (section 3.1). The power was recalculated based on the reduced sample size following the original assumptions descriped above.

> After randomizing 130 subjects in each of the two treatment arms, for a total of 260 randomized subjects and assuming a 10% drop out rate, 119 subjects per group are expected to complete the study.
>
> Assuming a common standard deviation (SD) in the change from baseline (Day 1) to Day 57 for CCSS of [redacted] a sample size of 119 evaluable subjects per group will have 98.7% power to detect a difference of [redacted] between the active treatment group and the placebo group at a significance level of 0.05.

6. Data Preparation

All the datasets used for the analyses and presentations of summary results will be implemented using Clinical Data Interchange Standards Consortium (CDISC, Implementation Guide [IG] Version 3.2) and the analysis data model (ADaM, Implementation Guide [IG] Version 2.0) format. The ADaM datasets will be created using SDTM datasets.

7. Analysis Populations

The following analysis populations will be considered:

7.1 Intent-to-Treat (ITT) Population

The ITT population includes all randomized subjects. The primary analysis will be performed on the ITT population with the primary estimand detailed in Section 2.6 of this SAP. Subjects in the ITT population will be analyzed as randomized.

7.2 Per Protocol (PP) Population

The PP population includes subjects in the ITT population who do not have significant protocol deviations. Protocol deviations will be assessed prior to database lock and unmasking. The PP population will be analyzed using observed data only for efficacy variables. Subjects in the PP population will be analyzed as treated.

7.3 Safety Population

The Safety population includes all randomized subjects who have received at least one dose of the investigational product (IP). The Safety population will be analyzed for all safety assessments. Subjects in the Safety population will be analyzed as treated.

8. General Statistical Considerations

8.1 Unit of Analysis

Safety endpoints will be analyzed for both eyes. For subject-level efficacy endpoints, the unit of analysis will be the subject. For eye-level efficacy endpoints, the unit of analysis will be the study eye as defined by the following:

Study Eye: Eyes are eligible for analysis if they meet all of the inclusion criteria. In the case that both eyes are eligible for analysis, the study eye will be the eye with worse (higher) central corneal fluorescein staining score at Day 1. If the central corneal fluorescein staining score is the equivalent in both eyes, then the right eye will be selected as the study eye.

8.2 Missing or Inconclusive Data Handling

The primary efficacy analyses will be performed using the multiple imputation methodology specified in Estimand 1. If the rate of missing data for EDS-VAS is imbalanced between treatment groups, then trimmed means methodology will be executed as specified in Estimand 2. Full descriptions of Estimands 1 and 2 are provided in Section 2.6 of this SAP. Additional sensitivity and supportive analyses may be executed, including:

- Multiple imputation via placebo group-based pattern-mixture model (PMM) imputation with the ITT population under the assumption of missing not at random for all missing.
- A tipping point sensitivity analysis with corresponding imputations of increasingly more conservative “penalties” added to the active group PMM imputatons, until such point that the treatment group difference is no longer significant.
- Multiple imputation via randomized treatment group-based Markov Chain Monte Carlo (MCMC) with the ITT population under the assumption of missing at random for all missing.
- Last observation carried forward (LOCF) imputation methodology using the ITT population.
- Observed data only using ITT and PP populations.

No secondary efficacy endpoints or safety endpoints will be imputed.

8.3 Definition of Baseline

Baseline measures are defined as the last measure prior to the initiation of study treatment, usually at Day 1.

8.4 Data Analysis Conventions

All data analyses will be performed after the study is completed and the database has been locked and released for unmasking. Statistical programming and analyses will be performed using SAS® Version 9.4 or higher. Output will be provided in RTF (rich text format) for tables, listings, and figures using landscape orientation. All study data will be listed by subject, treatment, and visit (as applicable) based on all enrolled subjects unless otherwise specified.

All summaries will be presented by treatment group and visit where appropriate, unless otherwise specified. Listings will be presented for all data collected on the eCRFs, sorted by subject id number and visit.

Summaries for continuous and ordinal variables will include the number of observations (n), arithmetic mean, SD, median, minimum, and maximum. Minima and maxima will be reported with the same precision as the raw values; means and medians will be presented to one additional decimal place than reported in the raw values. Standard deviations will be presented to two additional decimal places than reported in the raw values. Summaries for discrete variables will include frequency counts and percentages. All percentages will be rounded to one decimal place (i.e., XX.X%).

All statistical tests will be two-sided with a significance level of 0.05 ($\alpha = 0.05$) unless otherwise specified. Confidence intervals (CI) will be two-sided at 95% confidence levels where appropriate. All p-values will be rounded to four decimal places; p-values less than 0.0001 will be presented as "<0.0001"; p-values greater than 0.9999 will be presented as ">0.9999."

8.5 Adjustments for Multiplicity

Hierarchical fixed sequence testing will be used to maintain the type I error rate. The primary analysis will first test the difference in CFB (Day 1) of CCSS in the study eye at Day 57 in the ITT population using the primary estimand. If the test of the difference between treatment groups is statistically significant at the two-sided alpha = 0.05 level in favor of Tanfanercept, then the study will be considered a success, Tanfanercept will be declared to be superior to placebo in the change from baseline (Day 1) of CCSS at Day 57, and the difference in the change from baseline (Day 1) of EDS at Day 57 will then be tested at the two-sided alpha = 0.05 level in the ITT population.

If, in addition to a statistically significant test of the difference in change from baseline (Day 1) of CCSS in the study at Day 57 in favor of Tanfanercept, the test of the difference in the change from baseline (Day 1) of EDS at Day 57 in the ITT population with the primary estimand is also statistically significant in favor of Tanfanercept, then Tanfanercept will be declared superior to placebo in both the change from baseline (Day 1) of CCSS and the change from baseline (Day 1) of EDS at Day 57.

Secondary efficacy analyses will not be type-I error controlled and will be considered hypothesis generating.

9. Disposition

9.1 Subject Disposition

Subject disposition will be presented in terms of the numbers and percentages of subjects who completed the study and discontinued from the study. Subjects who are not discontinued from the study will be considered study completers. Disposition will be summarized by treatment group and for all subjects. The total number of screened subjects with the number and percentage of screen failure subjects will be summarized as well.

The number of randomized subjects in each analysis population (ITT, PP, and Safety) will be displayed by treatment. The ITT population uses treatment as randomized; PP and Safety populations use treatment as treated. Percentages are based on the total number of subjects randomized in each treatment group.

The number and percentage of subjects prematurely discontinued from the study and the reasons for study discontinuation will be summarized by treatment group for all randomized subjects. The reasons for study discontinuation that will be summarized include: Pregnancy, AE, Lack of Efficacy, Unmasking When Medically Necessary, Protocol Violation, Administrative Reasons (e.g., Inability to Continue, Lost to Follow Up), Study Termination by Sponsor, Subject Choice, and Other. A subject listing of disposition will be provided that includes the date of and reason for premature study discontinuation.

9.2 Protocol Deviations

The number and percentage of subjects with any, major, and minor protocol deviations will be summarized by treatment group for all randomized subjects. The number and percentage of subjects with any protocol deviation will also be summarized for the following categories: Informed Consent, Inclusion / Exclusion and Randomization, Test Article / Study Drug Instillation and Assignment at Site, Improper Protocol Procedures at Site, Site's Failure to Report Serious Adverse Event (SAE) / AE, Visit Out of Window, Subject's Non-compliance with Test Article, Subject's Use of Prohibited Concomitant Medication, Subject's Failure to Follow Instructions, and Other. A subject listing will be provided that includes the date, visit at which the deviation occurred (if applicable), deviation code, description of each deviation, whether the deviation was COVID-19 related, and the classification of whether the deviation was judged to be major or minor.

In addition, subject listings will be provided that include date of randomization, randomization number, randomization arm, actual treatment, and [redacted] whether inclusion and exclusion criteria were met, and inclusion in the analysis populations. A listing of subjects affected by COVID-19 discontinuations and protocol deviations will be generated as well.

A table summarizing the number of randomized subjects enrolled by site with percentages will be generated.

10. Demographic and Pretreatment Variables

10.1 Demographic Variables

The demographic variables collected in this study include age, sex, race, ethnicity, and iris color. Demographic variables will be summarized for the ITT and Safety populations separately.

Age (years) will be summarized, overall and by treatment, using continuous descriptive statistics. Age will also be categorized as follows: <65 years and ≥65 years. Age will be reported in years and calculated using the following formula:

Age = (Informed Consent Date – Date of Birth) / 365.25, truncated as an integer

The number and percentage of subjects will be presented, overall and by treatment, for age category, sex, race, ethnicity, iris color for the right eye (OD) and left eye (OS), [redacted]

A subject listing that includes all demographic variables will be provided.

10.2 Pretreatment Variables

Baseline disease characteristics will be summarized by treatment group using continuous descriptive statistics for central corneal staining score (CCSS), eye dryness score (EDS), total OSDI© score, unanesthetized Schirmer's test, best-corrected visual acuity (BCVA), and IOP. All summaries will be for the study eye, except for OSDI© which is a subject-level assessment. The scale for each assessment is provided in the variables' respective subsections in Section 13.2 of this SAP. Baseline disease characteristics will be displayed for the ITT population.

11. Medical History and Concomitant Medications

11.1 Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 24.0.

Medical history will be summarized using counts and percentages and presented by treatment group at the subject and event level by System Organ Class (SOC) and Preferred Term (PT) using the ITT population. If a subject reports the same PT multiple times within the same SOC, that PT will only be reported once within that SOC. As with the PT, if a subject reports multiple conditions within the same SOC, that SOC will only be reported once. In the summaries, SOCs and PTs within an SOC are presented in ascending alphabetical order.

Listings of medical history will be generated separately for ocular and non-ocular data.

11.2 Prior and Concomitant Medications

Ocular and non-ocular prior and concomitant medications will be coded using World Health Organization Drug Dictionary (WHODrug) Global B3 (March 2021) and coded to the therapeutic drug class (Anatomical Therapeutic Chemical [ATC] 4 classification) and preferred name.

Concomitant medications are defined as those medications listed as having been taken (1) prior to initiation of randomized study drug administration (Day 1) and continuing for any period of time following the first administration of randomized study drug or (2) at any time following the first administration of randomized study drug (Day 1). Prior medications are reported medications that have been taken prior to and not on or after initiation of randomized study drug administration.

Concomitant medications will be summarized using the Safety population. Prior medications will not be included in data summaries, but will provided on data listings. Concomitant medications will be tabulated for each treatment group and for all subjects using frequencies and percentages. Subjects may have more

than 1 medication per ATC class. At each level of subject summarization, a subject will be counted once if he/she reports 1 or more medications. Percentages will be based on the number of subjects in each treatment group. In the summaries, ATC classes and preferred names within an ATC class are ordered by descending frequency values based on all subjects.

Listings of concomitant and prior medications will be generated separately for ocular and non-ocular data.

11.3 Concomitant Procedures

Concomitant procedures will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 24.0.

Concomitant procedures will be summarized using discrete summary statistics and presented by treatment group at the subject and event level by System Organ Class (SOC) and Preferred Term (PT) using the ITT population. If a subject reports the same PT multiple times within the same SOC, that PT will only be reported once within that SOC. As with the PT, if a subject reports multiple conditions within the same SOC, that SOC will only be reported once. In the summaries, SOCs and PTs within an SOC are presented in ascending alphabetical order.

Listings of concomitant procedures will be generated separately for ocular and non-ocular data.

12. Dosing Compliance and Treatment Exposure

12.1 Dosing Compliance

Dosing compliance will be calculated as:

Dosing Compliance (%) = (Number of doses taken from Day 1 to study completion/discontinuation visit / Number of expected doses from Day 1 to study completion/discontinuation visit) * 100

The number of doses taken will be calculated by subtracting the number of unused vials from the number of vials dispensed plus the total number of vials missed reported in the electronic case report form (eCRF). For subjects who do not receive a dose of randomized study drug, the number of expected doses will be 0 and compliance will be defined as 0. Otherwise, the number of expected doses will be calculated as 2 x [Date of Study Completion/Discontinuation – Date of Day 1 +1]. If a subject discontinues on Day 1 then the number of expected doses is 1.

Dosing compliance will be summarized using continuous descriptive statistics including mean, SD, median, minimum, and maximum for the Safety Population. Additionally, a categorical summary display frequencies and percentages of those deemed compliant, under-compliant (<80%), and over-compliant (>125%).

12.2 Treatment Exposure

Extent of treatment exposure for completed or discontinued subjects will be calculated in days using the following:

Extent of Exposure (days) = (Date of Study Completion/Discontinuation – Date of Day 1) + 1

Extent of treatment exposure (days) for each subject exposed to study drug will be summarized with continuous descriptive statistics for each treatment group, using the Safety population. A subject listing of treatment exposure and dosing compliance will also be produced.

13. Efficacy Analyses

13.1 Primary Analyses

The primary efficacy endpoints of this study include mean CFB to Day 57 of central corneal staining score (CCSS) and eye dryness score on Visual Analog Scale (EDS-VAS).

CCSS will be graded using the Ora Calibra® Corneal and Conjunctival Fluorescein Staining Scale. The Ora Calibra® Corneal and Conjunctival Staining Scale ranges from [redacted]

EDS will be subjectively graded by the subjects using the VAS at all scheduled visits. Subjects are asked to rate each ocular symptom due to ocular dryness by placing a vertical mark on the horizontal line to indicate the current level of discomfort. 0% corresponds to “no discomfort” and 100% corresponds to “maximal discomfort.”.

For both endpoints, CFB to each post-baseline protocol visit (Section 3.1) will be calculated using actual scores and resulting scores from multiple imputation methodology specified in Estimand 1 (Section 2.6). The imputation methods will be performed using the SAS® procedure PROC MI. Refer to Appendix 1 for examples of SAS® codes for obtaining randomized treatment group-based MCMC multiple imputation data.

CFB to a post-baseline visit timepoint will be calculated as Post-baseline visit result minus Baseline visit results

Note: Positive difference indicates a worsening of dry eye signs or symptoms. In addition, treatment comparisons between active and placebo will be calculated as Active minus Placebo, such that a negative result indicates a better score for the active treatment (i.e., tanfanercept group demonstrated less severity in dry eye signs or symptoms than the placebo group).

13.1.1 Central Corneal Staining Score (CCSS)

CCSS CFB to Day 57 will be analyzed using the ITT population with multiple imputation methodology specified in Estimand 1 (Section 2.6). The initial MMRM model will include terms for baseline CCSS, site, visit (as categorical term), treatment group and the interaction of treatment group and visit as fixed effects with correlated errors. The inclusion of site in the final model will be evaluated at an alpha level of 0.1. All post-baseline visits will be used in the model.

If site is retained in the final primary analyses, the site by treatment interaction will be explored in a separate analysis to evaluate how the treatment effect may differ across sites. All post-baseline visits will be used in the model.

An alternate MMRM will be executed as supportive analysis. This additional model will include all terms in the final model of the primary analyses with, [redacted]

Sensitivity analyses to compare CCSS CFB between treatment groups using imputation by Last Observation Carried Forward (LOCF), multiple imputation by placebo group-based pattern mixture models (PMM), and analyses of observed data only using the ITT and PP populations will be conducted.

The Least Square (LS) means, LS mean difference, Standard Errors (SEs), two-sided 95% CIs, and p-values of the LS mean difference will be reported from the MMRM model. Two-sample t-tests will also be conducted as supportive analyses of the mean CFB to Day 57. The sample means, sample mean difference, SEs, two-sided 95% CIs, and two-sided p-values will be reported from the two-sample t-test.

The MMRM LS means of the CCSS CFB in the study eye at Day 57 and CCSS CFB at each visit will be displayed graphically in a bar chart with SE bars by treatment group.

13.1.2 Eye Dryness Score on Visual Analog Scale (EDS-VAS)

EDS-VAS CFB to Day 57 will be analyzed as described above for the analysis of CCSS with adjustment for baseline EDS-VAS instead of CCSS. Estimand 2 will be used for the analysis of EDS-VAS in the presence of an imbalance of missing data between the two treatment groups (Section 2.6).

13.2 Secondary Analyses

The following secondary efficacy endpoints will be tested:

- Fluorescein staining (Ora Calibra® scale) by region: central, superior, inferior, temporal, nasal, corneal sum, conjunctival sum, and total staining
- Lissamine green staining (Ora Calibra® scale) by region: central, superior, inferior, temporal, nasal, corneal sum, conjunctival sum, and total staining
- Conjunctival Redness
- Unanesthetized Schirmer's Test
- TFBUT
- VAS
- OSDI©
- Ora Calibra® Ocular Discomfort Scale
- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire

- Ora Calibra® Drop Comfort assessment

13.2.1 Analyses of Secondary Endpoints

Actual scores will be summarized by visit and region/symptom using quantitative summary statistics. Two-sample t-tests will be employed to compare active treatment and placebo means of actual scores at each visit. The differences in samples means, SEs, two-sided 95% CIs for the difference in means and p-values will be reported.

Changes from baseline at each post-baseline visit will be summarized similarly. Analysis of the change from baseline at each post-baseline visit will utilize MMRM models similar to the primary analysis (substituting appropriate baseline and week variables) using observed data, The LS means, LS mean differences, SEs, two-sided 95% CIs for the difference in means and two-sided p-values will be reported from the models. Two sample t-tests will also be conducted. Within each treatment arm, paired t-tests will be conducted for changes from baseline. Analyses will be performed on the ITT population with observed data only. For assessments on both eyes, only the study eye will be analyzed and summarized.

Subject listings of each secondary efficacy assessment will be generated.

13.2.2 Fluorescein Staining

Corneal and conjunctival fluorescein staining will be performed at all scheduled visits, on both eyes and graded using the Ora Calibra® Corneal and Conjunctival Staining Scale. The scale will grade the cornea and conjunctiva by five regions: inferior, superior, central, temporal, and nasal. The Ora Calibra® Corneal and Conjunctival Staining Scale ranges from [redacted]The corneal sum score will be the sum of scores from the inferior, superior, and central regions. The conjunctival sum score will be the sum of scores from the nasal and temporal regions. The total eye score will be the sum of scores from all five regions.

Fluorescein staining scores will be summarized and analyzed by visit and region including sums as described in section 13.2.1.

Sample means of the fluorescein staining scores in the study eye will be displayed graphically in a line chart with SE bars by visit and treatment group for each region or sum separately.

13.2.3 Lissamine Green Staining

Corneal and conjunctival lissamine green staining will be performed at all visits, on both eyes and graded using the Ora Calibra® Corneal and Conjunctival Staining Scale. The scale will grade the cornea and conjunctiva by five regions: inferior, superior, central, temporal, and nasal. The Ora Calibra® Corneal and Conjunctival Staining Scale ranges from [redacted]The corneal sum score will be the sum of scores

from the inferior, superior, and central regions. The conjunctival sum score will be the sum of scores from the nasal and temporal regions. The total score will be the sum of scores from all five regions.

Lissamine green staining scores will be summarized and analyzed by visit and region including sums as described in section 13.2.1.

Sample means of the lissamine green staining scores in the study eye will be displayed graphically in a line chart with SE bars by visit and treatment group for each region or sum separately.

13.2.4 Conjunctival Redness

The Ora Calibra® Conjunctival Redness Scale for Dry Eye will be performed on all scheduled visits. The conjunctival redness scale ranges from [redacted]

Conjunctival redness scores will be summarized and analyzed by visit as described in section 13.2.1.

13.2.5 Unanesthetized Schirmer's Test

Unanesthetized Schirmer's Test will be assessed on both eyes at Day -14, Day 1, Day 15, Day 29, and Day 57. The Schirmer's test strip will be placed in the lower temporal lid margin of each eye. After 5 minutes, the test strip will be removed and the length of the moistened area will be recorded in millimeters (mm) for each eye. Lower values indicate less tears produced in the eye.

Unanesthetized Schirmer's Test will be summarized and analyzed for the study eye by visit as described in section 13.2.1.

Sample means of the unanesthetized Schirmer's test scores in the study eye will be displayed graphically in a line chart with SE bars by visit and treatment group.

13.2.6 Tear Film Break-Up Time

Tear film break-up time will be measured at all scheduled visits on all scheduled visist in both eyes. For each eye, two measurements will be recorded in seconds and averaged unless the two measurements are > 2 seconds apart and are each < 10 seconds, in which case, a third measurement will be taken and the two closest of the three will be averaged and used for analyses. If the differences between two sequential pairs of measurements are the same (e.g., 3, 6, 9 seconds), then the median of the three readings will be used for analysis.

Tear film break-up time will be summarized and analyzed for the study eye by visit as described in section 13.2.1.

13.2.7 Visual Analog Scale of Ocular Dryness

At each visit, subjects will be asked to rate each ocular symptom due to ocular dryness by placing a vertical mark on the horizontal line to indicate the current level of discomfort. 0% corresponds to "no discomfort" and 100% corresponds to "maximal discomfort." Subjects are to evaluate their current ocular discomfort symptoms as experienced while completing the questionnaire. Reported symptoms include burning/stinging, itching, foreign body sensation, blurred vesion, eye dryness, photophobia, and pain.

Visual analog scale will be summarized and analyzed by visit and symptom as described in section 13.2.1.

Sample means of the VAS symtoms will be displayed graphically in a line chart with SE bars by visit and treatment group for each symptom separately.

13.2.8 Ocular Surface Disease Index©

The OSDI© is assessed on a scale of 0 to 100, with higher scores representing greater disability. The OSDI© asks the following 12 questions at the subject level:

Have you experienced any of the following during the last week?

1) Eyes that are sensitive to light?
2) Eyes that feel gritty?
3) Painful or sore eyes?
4) Blurred vision?
5) Poor vision?

Have problems with your eyes limited you in performing any of the following during the last week?

6) Reading?
7) Driving at night?
8) Working with a computer or bank machine (ATM)?
9) Watching TV?

Have your eyes felt uncomfortable in any of the following situations during the last week?

10) Windy conditions?
11) Places or areas with low humidity (very dry)?
12) Areas that are air conditioned?

OSDI© will be assessed at each visit at the subject level. The 5-unit scale for responses to the OSDI© is given by the following: [redacted] The total OSDI© score is calculated by the following:

$$\text{OSDI©} = \frac{\text{(Sum of Scores)} \times 25}{}$$

# of Questions Answered

Note that the number of questions answered in the denominator should exclude those questions with a response of "N/A."

OSDI© will be summarized and analyzed by visit and by question, subgroup, and total score as described in section 13.2.1.

13.2.9 ORA CALIBRA® OCULAR DISCOMFORT SCALE

Ocular discomfort scores will be subjectively graded by the subjects using the Ora Calibra® Ocular Discomfort Scale at all scheduled visits. The ocular discomfort scale ranges from [redacted]

Ocular Discomfort Scale will be summarized and analyzed by visit as described in section 13.2.1.

Sample means of the Ocular Discomfort Scale scores in the study eye will be displayed graphically in a line chart with SE bars by visit and treatment group.

13.2.10 ORA CALIBRA® OCULAR DISCOMFORT & 4-SYMPTOM QUESTIONNAIRE

Ocular discomfort and dry eye symptoms will be assessed at all scheduled visits at the subject level in regard to how both eyes feel. The Ora Calibra® Ocular Discomfort &[redacted]

Ocular Discomfort & 4-Symptom Questionnaire will be summarized and analyzed by visit as described in section 13.2.1.

Sample means of the symtoms from the Ocular Discomfort & 4-Symptom Questionnaire will be displayed graphically in a line chart with SE bars by visit and treatment group for each symptom separately.

14. Summary of Efficacy Analyses

A summary of all efficacy analyses will be presented. For MMRM models, treatment group LS means, LS mean differences, SEs for the LS mean differences, and p-values for the treatment group comparisons will be presented. For t-tests, treatment group sample means, sample mean differences, SEs for sample mean differences, and p-values for treatment group comparisons will be presented.

15. Safety Analyses

All safety analyses will be conducted using the Safety population.

15.1 Adverse Events

An AE is defined as any untoward medical occurrence associated with the use of IP in humans, whether or not considered IP-related. An AE can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IP, without any judgment about causality. An AE can arise from any use of the IP (e.g., off-label use, use in combination with another drug or medical device) and from any route of administration, formulation, or dose, including an overdose. All AEs will be coded using MedDRA Version 24.0.

Treatment-emergent adverse events (TEAEs) are defined as any event that occurs or worsens on or after the day that randomized study treatment is initiated.

An overall summary will be presented that includes the number of AEs, TEAEs, SAEs, treatment-emergent serious adverse events (TE-SAEs), number of subjects with TEAEs by maximum severity, and number of subjects with TEAEs by relationship to study drug. The summary will also include the number and percentage of subjects with treatment discontinuation due to an AE, the number and percentage of subjects with an AE resulting in death, and the number and percentage of subjects who experienced at least one AE, TEAE, SAE, and TE-SAE by treatment group and for all subjects. This summary will include breakdowns of AEs and TEAEs further categorized as ocular or non-ocular as well as the number and percentage of resolved ocular AEs and the mean and SD number of days until AE resolution for resolved ocular AEs.

Additional summaries of TEAEs will be provided showing the number and percentage of subjects who experienced at least one TEAE. These summaries will be presented by SOC and PT. Non-ocular TEAEs will be summarized using discrete summary statistics and presented by treatment group at the subject and event level by SOC and PT. Ocular TEAEs will be similarly summarized at the subject and event level by SOC and PT. If a subject reports the same PT multiple times within the same SOC, that PT will only be reported once within that SOC. As with the PT, if a subject reports multiple conditions within the same SOC, that SOC will only be reported once. In the summary, SOC will be listed in order of descending frequency for all subjects; PTs will be listed in order of descending frequency for all subjects within each SOC.

Conjunctivitis AEs will also summarized by number of AEs and number and percentages of subjects who experienced at least one conjunctivitis AE. Categories of conjunctivitis AEs (bacterial, viral, and hypersensitivity) will be further summarized as described. Additionally, the number of subjects with a conjunctivitis AE that experience any of the following symptoms will be summarized:

- Injected Sclera
- Redness
- Burning
- Eye Discharge
- Unusual Crusting on Eye When Awakening

- Ocular Itchiness
- Nasal Itchiness
- Sneezing
- Excessive Tearing
- Other Signs or Symptoms.

A subject listing of conjunctivitis AEs will be generated for all randomized subjects.

Additionally, separate summaries will be provided for the following categories of AEs:

- Ocular AEs
- Non-ocular AEs
- Ocular TEAEs
- Non-ocular TEAEs
- Ocular treatment-related TEAEs
- Non-ocular treatment-related TEAEs
- SAEs

Severity of an AE is defined as a qualitative assessment of the degree of intensity of an AE as determined by the Investigator or reported to him/her by the subject. The assessment of severity is made irrespective of relationship to study drug or seriousness of the event and should be evaluated according to the following scale:

- *Mild:* Event is noticeable to the subject, but is easily tolerated and does not interfere with the subject's daily activities.
- *Moderate:* Event is bothersome, possibly requiring additional therapy, and may interfere with the subject's daily activities.
- *Severe*: Event is intolerable, necessitates additional therapy or alteration of therapy, and interferes with the subject's daily activities.

Summaries of TEAEs by maximal severity will be presented for ocular AEs and non-ocular AEs separately. The number of subjects with any TEAEs (along with percentages) will be tabulated by SOC and PT within each SOC by treatment group. To count the number of subjects with any TEAEs, if a subject has multiple TEAEs coded to the same PT within the same SOC, the subject will be counted once under the maximal severity.

The occurrence of non-ocular and ocular TEAEs will also be tabulated by SOC, PT, and study day of onset (prior to Day 9, Day 9 to Day 29, After Day 29).

The relationship of each AE to the IP should be determined by the investigator (in a masked manner) using these explanations:

- ***Suspected****:* A reasonable possibility exists that the IP caused the AE. A suspected AE can be further defined as:
    - *Definite:* Relationship exists when the AE follows a reasonable sequence from the time of IP administration, follows a known response pattern of the drug class, is confirmed by improvement on stopping the IP and no other reasonable cause exists.
    - *Probable:* Relationship exists when the AE follows a reasonable sequence from the time of IP administration, follows a known response pattern of the drug class, is confirmed by improvement on stopping the IP and the suspect IP is the most likely of all causes.
    - *Possible:* Relationship exists when the AE follows a reasonable sequence from the time of administration, but could also have been produced by the subject's clinical state or by other drugs administered to the subject.
- ***Not Suspected***: A reasonable possibility does not exist that the IP caused the AE. A not suspected AE can further be defined as:
    - *Not Related:* Concurrent illness, concurrent medication, or other known cause is clearly responsible for the AE, the administration of the IP and the occurrence of the AE are not reasonably related in time, OR exposure to IP has not occurred.

All possible, probable, and definite TEAEs are considered as treatment-related TEAEs.

All AEs will be presented in a subject listing for all screened subjects. Separate listings will be produced for Conjunctivitis AEs, SAEs, AEs leading to treatment discontinuation, and AEs leading to death for all randomized subjects.

15.2 Visual Acuity (VA)

The VA procedure will be performed at each scheduled visit. The logarithm of the minimum angle of resolution (logMAR) VA must be assessed using an Early Treatment of Diabetic Retinopathy Study (ETDRS) chart. The procedure used will be consistent with the recommendations provided for using the ETDRS eye chart. Visual Acuity should be evaluated at the beginning of each visit in the study (i.e., prior to slit-lamp examination). Subjects should use their most recent correction to attain their best-corrected visual acuity (BCVA).

The observed VA and change from baseline in VA will be summarized for each eye (study eye and fellow eye) using continuous descriptive statistics by visit for each treatment group. The number and percentage of subjects who had logMAR change from baseline ≥ +0.22 will be summarized for each eye by treatment group. The worst on-treatment value also will be summarized, and the CFB for the worst on-treatment value will be summarized analogously.

A subject listing of VA will also be produced.

15.3 Slit-Lamp Biomicroscopy Examination

A slit-lamp biomicroscopy examination of the cornea, conjunctiva, anterior chamber, iris, lens, and eyelid will be performed at each visit. The results will be graded as Normal, Abnormal Not Clinically Significant (NCS), or Abnormal Clinically Significant (CS). Abnormal findings will be described.

The results will be summarized using counts and percentages for each treatment group at each visit for each eye (study eye and fellow eye). Percentages will be based on the number of subjects in each treatment group with responses. Shift tables for the slit-lamp biomicroscopy parameters will also be provided comparing each follow-up visit to baseline. The worst on-treatment value and the shift from baseline for the worst on-treatment value also will be summarized.

A subject listing of the slit-lamp biomicroscopy parameters will also be produced.

15.4 Dilated Fundoscopy Examination

A dilated fundoscopy exam will be performed during the study at Day -14 and Day 57, and potentially at unscheduled visit assessments. Observations of the vitreous, retina, macula, choroid, and optic nerve will be graded as Normal, Abnormal NCS, or Abnormal CS. Abnormal findings will be described.

The results will be summarized using counts and percentages for each treatment group at each visit for each eye (study eye and fellow eye). Percentages will be based on the number of subjects in each treatment group with responses. Shift tables for the dilated fundoscopy parameters will also be provided comparing Day 57 to baseline. The worst on-treatment value and the shift from baseline for the worst on-treatment value also will be summarized.

A subject listing of the dilated fundoscopy parameters will also be produced.

15.5 Intraocular Pressure (IOP)

Intraocular pressure will be measured in each eye by contact tonometry by the examiner and the results will be recorded in mmHg at Day -14 and Day 57. A single measurement is made to obtain a determination of IOP. The same tonometer employing the investigator's standard technique will be used throughout the study. In addition, all reasonable efforts will be made to have the same examiner obtain all IOP measurements for a given subject.

The IOP values and changes from baseline for each eye (study eye and fellow eye) will be summarized using continuous descriptive statistics by visit and eye for each treatment group. The worst on-treatment value also will be summarized, and the CFB for the worst on-treatment value will be summarized analogously.

A subject listing of IOP will also be produced.

15.6 Immunogenicity to Tanfanercept Ophthalmic Solution 0.25% in Serum

Serum blood draws will be collected at Day 1, Day 29, and Day 57 for immunogenicity testing. Instructions for the collection, handling, and shipping of blood for immunogenicity testing are given in a separate laboratory manual. Analyses of immunogenicity data will be conducted as ad-hoc analyses. The anticipated ad-hoc analyses of immunogenicity are as follows.

Immunogenicity will be summarized using discrete summary statistics. Counts and proportions of subjects with anti-drug antibodies (ADA) will be presented by visit and treatment group. Exact 95% Clopper-Pearson CIs will be presented. Treatment groups will be compared using Fisher's exact test, and exact 95% confidence intervals for the pairwise proportion differences will be constructed.

Antibody titer of subjects positive for ADA will be summarized using continuous descriptive statistics and presented by visit and treatment group. Treatment groups will be compared using two-sample t-tests. The differences in means, two-sided 95% CIs for the difference in means, and p-values will be reported.

16. Other Endpoints

16.1 Ora Calibra® Drop Comfort Scale and Questionnaire

16.1.1 Ora Calibra® Drop Comfort Scale

Drop comfort will be assessed for each eye immediately upon instillation, and at 1 and 2 minutes following initial dosing at Day 1 and Day 8 using the Ora Calibra® Drop Comfort Scale. [redacted] Drop comfort will be summarized by visit and time point using quantitative summary statistics. Two-sample t-tests will be employed to compare the actual scores of the active treatment and placebo. The differences in means, SEs, two-sided 95% CIs for the difference in means, and p-values will be reported. Analyses will be performed on the ITT population with observed data only for the study eye.

16.1.2 Ora Calibra® Drop Comfort Questionnaire

Descriptions of drop comfort will be assessed at 3 minutes following initial dosing at Day 1 and Visit 3 (Day 8) using the Ora Calibra® Drop Comfort Questionnaire. On this questionnaire, subjects will be asked to choose three words that best describe how each eye drop feels in both of his/her eyes. [redacted] Subjects may also select "other" and write in a response of their choosing, which may be either a positive or a negative response. Drop Comfort Questionnaire responses will be summarized by treatment group using qualitative summary statistics. Subjects with at least one negative response as well as subjects with at least one positive response will also be summarized by treatment group. Analyses will be performed on the ITT population with observed data only.

17. Interim Analyses

No interim analyses are planned for this study.

18. Changes from Protocol-Stated Analyses

There are no changes from the protocol-stated analyses.

19. References

1. Permutt T, Li F. Trimmed means for symptom trials with dropouts. Pharm Stat, 2017; 16(1): 20-8.

20. Revision History

Revision history will be documented for any change in the organization responsible for SAP authorship and after the final execution of Version 1.0 of this SAP.

21. Tables

Ten tables that will be included in the topline delivery are shown in boldface font.

[1,2] One of the two sets of primary endpoint tables will be delivered with topline according primary estimand defined in section 2.6.

Table Number	Title	Population
Table 14.1.1	**Subject Disposition**	**All Randomized Subjects**
Table 14.1.2.1	**Demographics**	**ITT Population**
Table 14.1.2.2	Demographics	Safety Population
Table 14.1.3.1	**Baseline Disease Characteristics (Study Eye)**	**ITT Population**
Table 14.1.4.1	Ocular Medical History	ITT Population
Table 14.1.4.2	Non-Ocular Medical History	ITT Population
Table 14.1.5.1	Ocular Concomitant Medications by Treatment Group, Drug Class, and Preferred Name	ITT Population
Table 14.1.5.2	Non-Ocular Concomitant Medications by Treatment Group, Drug Class, and Preferred Name	ITT Population
Table 14.1.6.1	Ocular Concomitant Procedures	ITT Population
Table 14.1.6.2	Non-Ocular Concomitant Procedures	ITT Population
Table 14.1.7	Subject Pooling by Site	All Randomized Subjects
Table 14.2.1.1	**Central Corneal Fluorescein Staining (Ora Calibra Scale) at Visit 6 (Day 57)**	**ITT Population with Multiple Imputation**

Table Number	Title	Population
		Methodology (Estimand 1)[1]
Table 14.2.1.2	**Central Corneal Fluorescein Staining (Ora Calibra Scale) at Visit 6 (Day 57): Permutation Test with Trimmed Means**	**ITT Population with Single Imputation Methodology (Estimand 2)[1]**
Table 14.2.1.3	Central Corneal Fluorescein Staining (Ora Calibra Scale) at Visit 6 (Day 57)	ITT Population with PMM
Table 14.2.1.4	Central Corneal Fluorescein Staining (Ora Calibra Scale) at Visit 6 (Day 57)	ITT Population with MCMC
Table 14.2.1.5	Central Corneal Fluorescein Staining (Ora Calibra Scale) at Visit 6 (Day 57)	ITT Population with LOCF
Table 14.2.1.6	Central Corneal Fluorescein Staining (Ora Calibra Scale) at Visit 6 (Day 57)	ITT Population with Observed Data Only
Table 14.2.1.7	Central Corneal Fluorescein Staining (Ora Calibra Scale) at Visit 6 (Day 57)	PP Population with Observed Data Only
Table 14.2.1.1.1	Central Corneal Staining Score (Ora Calibra Scale) at Visit 6 (Day 57) – Site Analysis	ITT Population with Multiple Imputation (Estimand 1)
Table 14.2.2.1	**Eye Dryness Score (Visual Analog Scale) at Visit 6 (Day 57)**	**ITT Population with Multiple Imputation Methodology (Estimand 1)[2]**
Table 14.2.2.2	**Eye Dryness Score (Visual Analog Scale) at Visit 6 (Day 57): Permutation Test with Trimmed Means**	**ITT Population with Single Imputation Methodology (Estimand 2)[2]**
Table 14.2.2.2	Eye Dryness Score (Visual Analog Scale) at Visit 6 (Day 57)	ITT Population with PMM
Table 14.2.2.3	Eye Dryness Score (Visual Analog Scale) at Visit 6 (Day 57)	ITT Population with MCMC
Table 14.2.2.4	Eye Dryness Score (Visual Analog Scale) at Visit 6 (Day 57)	ITT Population with LOCF

Table Number	Title	Population
Table 14.2.2.5	Eye Dryness Score (Visual Analog Scale) at Visit 6 (Day 57)	ITT Population with Observed Data Only
Table 14.2.2.6	Eye Dryness Score (Visual Analog Scale) at Visit 6 (Day 57)	PP Population with Observed Data Only
Table 14.2.2.1.1	Eye Dryness Score (Visual Analog Scale) at Visit 6 (Day 57) – Site Analysis	ITT Population with Multiple Imputation Methodology (Estimand 1)
Table 14.2.3	**Fluorescein Corneal and Conjunctival Staining (Ora Calibra Scale)**	**ITT Population with Observed Data Only**
Table 14.2.4	Lissamine Green Corneal and Conjunctival Staining (Ora Calibra Scale)	ITT Population with Observed Data Only
Table 14.2.5	Conjunctival Redness Scale (Ora Calibra Scale)	ITT Population with Observed Data Only
Table 14.2.6	Unanesthetized Schirmer's Test (mm)	ITT Population with Observed Data Only
Table 14.2.7	Tear Film Break-Up Time	ITT Population with Observed Data Only
Table 14.2.8	**Visual Analog Scale**	**ITT Population with Observed Data Only**
Table 14.2.9	Ocular Surface Disease Index (OSDI)	ITT Population with Observed Data Only
Table 14.2.10	Ocular Discomfort Scale (Ora Calibra Scale)	ITT Population with Observed Data Only
Table 14.2.11	Ocular Discomfort & 4-Symptom Questionnaire (Ora Calibra Scale)	ITT Population with Observed Data Only
Table 14.2.12	Summary of Efficacy Analyses	Multiple Populations
Table 14.3.1.1	**Overall Adverse Event Summary**	**Safety Population**
Table 14.3.1.2	All Conjunctivitis Adverse Events	Safety Population

Table Number	Title	Population
Table 14.3.1.3	All Ocular Adverse Events	Safety Population
Table 14.3.1.4	All Non-Ocular Adverse Events	Safety Population
Table 14.3.1.5	**All Ocular Treatment-Emergent Adverse Events**	**Safety Population**
Table 14.3.1.6	All Non-Ocular Treatment-Emergent Adverse Events	Safety Population
Table 14.3.1.7	All Ocular Treatment-Related Treatment-Emergent Adverse Events	Safety Population
Table 14.3.1.8	All Non-Ocular Treatment-Related Treatment-Emergent Adverse Events	Safety Population
Table 14.3.1.9	**All Serious Adverse Events**	**Safety Population**
Table 14.3.1.10	All Ocular Treatment-Emergent Adverse Events by Maximal Severity	Safety Population
Table 14.3.1.11	All Non-Ocular Treatment-Emergent Adverse Events by Maximal Severity	Safety Population
Table 14.3.1.12	All Ocular Treatment-Emergent Adverse Events by Study Day of Onset	Safety Population
Table 14.3.1.13	All Non-Ocular Treatment-Emergent Adverse Events by Study Day of Onset	Safety Population
Table 14.3.2	Visual Acuity (logMAR)	Safety Population
Table 14.3.3.1	Slit Lamp Biomicroscopy	Safety Population
Table 14.3.3.2	Shift in Slit Lamp Biomicroscopy	Safety Population
Table 14.3.4.1	Dilated Fundoscopy	Safety Population
Table 14.3.4.2	Shift in Dilated Fundoscopy	Safety Population
Table 14.3.5	Intraocular Pressure (mmHg)	Safety Population
Table 14.3.6.1	Ora Calibra Drop Comfort Scale	ITT Population with Observed Data Only

Table Number	Title	Population
Table 14.3.6.2	Ora Calibra Drop Comfort Questionnaire	ITT Population with Observed Data Only
Table 14.3.7	Compliance with Study Drug	Safety Population
Table 14.3.8	Exposure to Study Drug	Safety Population

22. Listings

Listing Number	Title	
Listing 16.1.7	Randomization Schedule	All Randomized Subjects
Listing 16.2.1	Subject Disposition	All Randomized Subjects
Listing 16.2.2	Protocol Deviations	All Screened Subjects
Listing 16.2.3.1	Study Population Inclusion	All Randomized Subjects
Listing 16.2.3.2	Inclusion/Exclusion and Screen Failures	All Screened Subjects
Listing 16.2.3.3	Subjects Affect By COVID-19	All Randomized Subjects
Listing 16.2.4.1	Demographics	All Screened Subjects
Listing 16.2.4.2	Ocular Medical History	All Randomized Subjects
Listing 16.2.4.3	Non-Ocular Medical History	All Randomized Subjects
Listing 16.2.4.4	Prior and Concomitant Ocular Medications	All Randomized Subjects

Listing Number	Title	
Listing 16.2.4.5	Prior and Concomitant Non-Ocular Medications	All Randomized Subjects
Listing 16.2.4.6	Ocular Concomitant Procedures	All Randomized Subjects
Listing 16.2.4.7	Non-Ocular Concomitant Procedures	All Randomized Subjects
Listing 16.2.5.1	In-Office Run-In and Study Drug Instillation	All Randomized Subjects
Listing 16.2.5.2	Run-In Kit Assignment and Replacement	All Randomized Subjects
Listing 16.2.5.3	Study Drug Kit Assignment and Replacement	All Randomized Subjects
Listing 16.2.5.4	Study Drug Accountability	All Randomized Subjects
Listing 16.2.5.5	Study Drug Exposure and Dosing Compliance	All Randomized Subjects
Listing 16.2.6.1	Fluorescein Corneal and Conjunctival Staining (Ora Calibra Scale)	All Randomized Subjects
Listing 16.2.6.2	Lissamine Green Corneal and Conjunctival Staining (Ora Calibra Scale)	All Randomized Subjects
Listing 16.2.6.3	Conjunctival Redness (Ora Calibra Scale)	All Randomized Subjects
Listing 16.2.6.4	Unanesthetized Schirmer's Test	All Randomized Subjects
Listing 16.2.6.5	Tear Film Break Up Time (TFBUT)	All Randomized Subjects
Listing 16.2.6.6	Visual Analog Scale	All Randomized Subjects

Listing Number	Title	
Listing 16.2.6.7	Ocular Surface Disease Index (OSDI)	All Randomized Subjects
Listing 16.2.6.8	Ocular Discomfort Scale (Ora Calibra Scale)	All Randomized Subjects
Listing 16.2.6.9	Ocular Discomfort & 4-Symptom Questionnaire (Ora Calibra Scale)	All Randomized Subjects
Listing 16.2.6.10	Ora Calibra Drop Comfort Scale	All Randomized Subjects
Listing 16.2.6.11	Ora Calibra Drop Comfort Questionnaire	All Randomized Subjects
Listing 16.2.7.1	All Adverse Events	All Randomized Subjects
Listing 16.2.7.2	Serious Adverse Events	All Screened Subjects
Listing 16.2.7.3	Adverse Events Leading to Treatment Discontinuation	All Randomized Subjects
Listing 16.2.7.4	Adverse Events Leading to Death	All Randomized Subjects
Listing 16.2.7.5	Conjunctivitis Adverse Events	All Randomized Subjects
Listing 16.2.8.1	Visual Acuity (logMAR)	All Randomized Subjects
Listing 16.2.8.2	Slit Lamp Biomicroscopy	All Randomized Subjects
Listing 16.2.8.3	Dilated Fundoscopy	All Randomized Subjects
Listing 16.2.8.4	Intraocular Pressure (IOP)	All Randomized Subjects

Listing Number	Title	
Listing 16.2.8.5	Blood Draw for Immunogenicity	All Randomized Subjects
Listing 16.2.8.6	Urine Pregnancy Test	All Randomized Subjects

23. Figures

Figure Number	Title	Population
Figure 14.2.1.1	**Change from Baseline of Central Corneal Fluorescein Staining (Ora Calibra Scale) at Visit 6 (Day 57)**	**ITT Population with Multiple Imputation Methodology (Estimand 1)**
Figure 14.2.2.1	**Change from Baseline of Eye Dryness Score (Visual Analog Scale) at Visit 6 (Day 57)**	**ITT Population with Multiple Imputation Methodology (Estimand 1)**
Figure 14.2.3	**Fluorescein Corneal and Conjunctival Staining (Ora Calibra Scale)**	**ITT Population with Observed Data Only**
Figure 14.2.4	Lissamine Green Corneal and Conjunctival Staining (Ora Calibra Scale)	ITT Population with Observed Data Only
Figure 14.2.5	Unanesthetized Schirmer's Test	ITT Population with

Figure Number	Title	Population
		Observed Data Only
Figure 14.2.6	**Visual Analog Scale**	**ITT Population with Observed Data Only**
Figure 14.2.7	Ocular Discomfort Scale (Ora Calibra Scale)	ITT Population with Observed Data Only
Figure 14.2.8	Ocular Discomfort & 4-Symptom Questionnaire (Ora Calibra Scale)	ITT Population with Observed Data Only

24. Appendix 1

The multiple imputation methodology will employ a combination of treatment group-based MCMC imputation and placebo-based PMM imputation. Imputation methods will be performed using the SAS® procedure PROC MI. The SAS® code for obtaining randomized treatment group-based MCMC multiple imputation data is:

```
PROC MI DATA = INDATA SEED = 425754 OUT = OUTDATA NIMPUTE = 30
      MINIMUM = 0 MAXIMUM = 4 ROUND = 0.5;
    BY TREATMENT;
    MCMC INITIAL = EM;
    VAR BASE V3 V4 V5 V6;
RUN;
```

where

- `INDATA` is the name of the input dataset
- `OUTDATA` is the name of the output dataset
- `TREATMENT` is the name of the treatment group variable
- [redacted]
- `V3 – V6` are the CCSS in the study eye at Visit 3 through Visit 6.

After obtaining 30 complete data sets and calculating changes from baseline, the following SAS® code will be used to run the MMRM model on each multiply imputed data set and combine the results from the 30 analyses:

```
PROC MIXED DATA = OUTDATA;
    BY _IMPUTATION_;
    CLASS TREATMENT;
    [redacted]
COVB;
    LSMEANS TREATMENT / CL PDIFF;
    ODS OUTPUT LSMEANS = OUTLS DIFFS = OUTDIFFS;
RUN;

PROC SORT DATA=OUTLS; BY TREATMENT _IMPUTATION_; RUN;

PROC MIANALYZE DATA=OUTLS;
    BY TREATMENT;
    MODELEFFECTS ESTIMATE;
    STDERR STDERR;
RUN;

PROC SORT DATA=OUTDIFFS; BY _IMPUTATION_; RUN;

PROC MIANALYZE DATA=OUTDIFFS;
    MODELEFFECTS ESTIMATE;
    STDERR STDERR;
RUN;
```

where

- TREATMENT is the name of the treatment group variable
- SITE is the study site id as a random effect

- BASELINE is the baseline CCSS in the study eye
- CFB is the change from baseline in CCSS in the study eye at Day 57
- OUTLS is the name of the output dataset that contains the statistical results for the treatment mean from the MMRM model that is run on each of the twenty imputation datasets
- OUTDIFFS is the name of the output dataset that contains the statistical results for the difference in treatment mean from the MMRM model that is run on each of the twenty imputation datasets

Similar SAS® code will be used to conduct MCMC multiple imputation analysis for the two sample t-test.

Furthermore, the SAS® code for obtaining the placebo-based PMM imputation data is:

```
PROC MI DATA = INDATA SEED = 988416 OUT = MDATA NIMPUTE = 30
      MINIMUM = 0 MAXIMUM = 4 ROUND = 0.5;
    MCMC IMPUTE=MONOTONE;
    VAR BASE V3 V4 V5 V6;
RUN;

PROC MI DATA = MDATA SEED = 253464 OUT = OUTDATA NIMPUTE = 1
      MINIMUM = . 0 0 0 0 0
      MAXIMUM = . 4 4 4 4 4
      ROUND = . 0.5 0.5 0.5 0.5 0.5;
    CLASS TREATMENT;
    MONOTONE REG(V6 = V5 V4 V3 BASE / DETAILS);
    MONOTONE REG(V5 = V4 V3 BASE / DETAILS);
    MONOTONE REG(V4 = V3 BASE / DETAILS);
    MONOTONE REG(V3 = BASE / DETAILS);
    MNAR MODEL(BASE V3 V4 V5 V6/ MODELOBS=(TREATMENT='Placebo'));
    VAR TREATMENT BASE V3 V4 V5 V6;
RUN;
```

where

- INDATA is the name of the input dataset
- MDATA is the name an intermediary dataset with a monotone missing pattern
- OUTDATA is the name of the output dataset
- TREATMENT is the name of the treatment group variable
- BASE is the baseline CCSS in the study eye
- V3 – V6 is the CCSS in the study eye at Visit 3 through Visit 6

An example of the SAS® code implementation of the MMRM model for the observed data only is as follows:

```
PROC MIXED;
```

```
        CLASS PATIENT WEEK TREATMENT;
        MODEL CFB = WEEK BASELINE TREATMENT / SOLUTION COVB;
        [redacted]
        LSMEANS TREATMENT / CL PDIFF;
RUN;
```

25. Appendix 2

Schedule of Visits and Assessments

Procedure	Screening Visit 1 (Day -14 ± 2)	Baseline Visit 2 (Day 1)	Visit 3 (Day 8 ± 1)	Visit 4 (Day 15 ± 2)	Visit 5 (Day 29 ± 2)	Visit 6 (Day 57 ± 3)	Visit 7-9[4]
Informed Consent / HIPAA	X						
Medical / Medication History and Demographics	X						
Placebo Run-In Collection		X					
Study Drug Collection			X	X	X	X	
Medical / Medication Update		X	X	X	X	X	X
Pregnancy Test	X[2]					X[2]	
Ocular Discomfort Scale	X	X	X	X	X	X	
Ocular Discomfort & 4-Symptom Questionnaire	X	X	X	X	X	X	
VAS	X	X	X	X	X	X	
OSDI© Questionnaire	X	X	X	X	X	X	
Visual Acuity (ETDRS)	X	X	X	X	X	X	
Slit Lamp Biomicroscopy	X	X	X	X	X	X	
Conjunctival Redness	X	X	X	X	X	X	
TFBUT	X	X	X	X	X	X	
Fluorescein Stainng	X	X	X	X	X	X	
Lissamine Green Staining	X	X	X	X	X	X	
Schirmer's Test	X	X		X	X	X	
Intraocular Pressure	X					X	
Dilated Fundus Exam	X					X	
Review of Qualification Criteria	X	X					

Placebo Run-In DIspensation and Instillation	X						
Blood Sampling for Immunogenicity		X			X	X	X
Randomization		X					
Study Drug Instillation		X	X				
Drop Comfort Scale		X	X				
Drop Comfort Questionnaire		X	X				
Adverse Event Query	X	X	X	X	X	X	X
Study Drug Dispensation		X[1]	X	X	X		
Exit Subject from Study						X[3]	

[1] The Visit 2 study drug kit is re-dispensed at Visit 3 (as each kit includes 2-week supply of study drug).
[2] To women of child-bearing potential.
[3] For subjects with negative immunogenicity results at Visit 6.
[4] Subjects will be asked to return for Blood Sample for Immunogenicity Testing if they test positive for immunogenicity at Visit 6. Visit 7 will occur approximately 6-12 months after Visit 6. If subject tests positive for immunogenicity at Visit 7, they will be asked to return for Visit 8 approximately 12 months after Visit 7. If subject tests positive for immunogenicity at Visit 8, subject will be asked to return for Visit 9 approximately 12 months after Visit 8.

DocuSign

Certificate Of Completion

Envelope Id: 0FD96C8D49AC44D78A4A23EF3B2091D1 Status: Completed

Subject: Complete with DocuSign: HanAll HL036-DED-US-P302 Statistical Analysis Plan Draft V1.0 23-JAN-20...

Source Envelope:

Document Pages: 45 Signatures: 3

Certificate Pages: 5 Initials: 0

AutoNav: Enabled

EnvelopeId Stamping: Disabled

Time Zone: (UTC-05:00) Eastern Time (US & Canada)

[redacted]

Record Tracking

Status: Original

1/23/2023 2:56:16 PM

[redacted]

Location: DocuSign

Signer Events	Signature	Timestamp
[redacted]	[redacted]	Sent: 1/23/2023 2:59:12 PM Viewed: 1/23/2023 2:59:36 PM Signed: 1/23/2023 2:59:57 PM
Veristat Security Level: Email, Account Authentication (Required), Logged in	Signature Adoption: Pre-selected Style Signature ID: EE88FE85-0D97-4568-AD83-AA0AFF1AFA3B Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I am the author of this document	
Electronic Record and Signature Disclosure: Accepted: 4/1/2022 9:54:26 AM ID: 560c4e3d-87cd-426c-baaf-86e528d82c8c		
[redacted]	[redacted]	Sent: 1/23/2023 2:59:13 PM Viewed: 1/23/2023 7:47:14 PM Signed: 1/23/2023 7:48:17 PM
Security Level: Email, Account Authentication (Required)	Signature Adoption: Pre-selected Style Signature ID: A2DE17C2-A041-44F2-A2CB-6EE2AA22005D Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	
Electronic Record and Signature Disclosure: Accepted: 1/16/2023 3:19:49 PM ID: 18699cc1-9ccc-4bde-8e7a-80f7fce26b71		

Signer Events	Signature	Timestamp
[redacted]	[redacted]	Sent: 1/23/2023 2:59:13 PM Viewed: 1/24/2023 12:09:52 PM Signed: 1/24/2023 12:10:48 PM
Veristat Security Level: Email, Account Authentication (Required)	Signature Adoption: Pre-selected Style Signature ID: 852EF035-F1A0-49D0-A0B9-BC5A9E7D5C0C Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I have reviewed this document	
Electronic Record and Signature Disclosure: Not Offered via DocuSign		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	1/23/2023 2:59:13 PM
Certified Delivered	Security Checked	1/24/2023 12:09:52 PM
Signing Complete	Security Checked	1/24/2023 12:10:48 PM
Completed	Security Checked	1/24/2023 12:10:48 PM

Payment Events	Status	Timestamps

Electronic Record and Signature Disclosure

Electronic Record and Signature Disclosure created on: 7/9/2020 3:25:19 PM
Parties agreed to [redacted]

ELECTRONIC RECORD AND SIGNATURE DISCLOSURE

From time to time, Veristat (we, us or Company) may be required by law to provide to you certain written notices or disclosures. Described below are the terms and conditions for providing to you such notices and disclosures electronically through the DocuSign system. Please read the information below carefully and thoroughly, and if you can access this information electronically to your satisfaction and agree to this Electronic Record and Signature Disclosure (ERSD), please confirm your agreement by selecting the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

Getting paper copies

At any time, you may request from us a paper copy of any record provided or made available electronically to you by us. You will have the ability to download and print documents we send to you through the DocuSign system during and immediately after the signing session and, if you elect to create a DocuSign account, you may access the documents for a limited period of time (usually 30 days) after such documents are first sent to you. After such time, if you wish for us to send you paper copies of any such documents from our office to you, you will be charged a $0.00 per-page fee. You may request delivery of such paper copies from us by following the procedure described below.

Withdrawing your consent

If you decide to receive notices and disclosures from us electronically, you may at any time change your mind and tell us that thereafter you want to receive required notices and disclosures only in paper format. How you must inform us of your decision to receive future notices and disclosure in paper format and withdraw your consent to receive notices and disclosures electronically is described below.

Consequences of changing your mind

If you elect to receive required notices and disclosures only in paper format, it will slow the speed at which we can complete certain steps in transactions with you and delivering services to you because we will need first to send the required notices or disclosures to you in paper format, and then wait until we receive back from you your acknowledgment of your receipt of such paper notices or disclosures. Further, you will no longer be able to use the DocuSign system to receive required notices and consents electronically from us or to sign electronically documents from us.

All notices and disclosures will be sent to you electronically

Unless you tell us otherwise in accordance with the procedures described herein, we will provide electronically to you through the DocuSign system all required notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you during the course of our relationship with you. To reduce the chance of you inadvertently not receiving any notice or disclosure, we prefer to provide all of the required notices and disclosures to you by the same method and to the same address that you have given us. Thus, you can receive all the disclosures and notices electronically or in paper format through the paper mail delivery system. If you do not agree with this process, please let us know as described below. Please also see the paragraph immediately above that describes the consequences of your electing not to receive delivery of the notices and disclosures electronically from us.

How to contact Veristat:

You may contact us to let us know of your changes as to how we may contact you electronically, to request paper copies of certain information from us, and to withdraw your prior consent to receive notices and disclosures electronically as follows:
To contact us by email send messages to: vincent.hughes@veristat.com

To advise Veristat of your new email address

To let us know of a change in your email address where we should send notices and disclosures electronically to you, you must send an email message to us at vincent.hughes@veristat.com and in the body of such request you must state: your previous email address, your new email address. We do not require any other information from you to change your email address.

If you created a DocuSign account, you may update it with your new email address through your account preferences.

To request paper copies from Veristat

To request delivery from us of paper copies of the notices and disclosures previously provided by us to you electronically, you must send us an email to vincent.hughes@veristat.com and in the body of such request you must state your email address, full name, mailing address, and telephone number. We will bill you for any fees at that time, if any.

To withdraw your consent with Veristat

To inform us that you no longer wish to receive future notices and disclosures in electronic format you may:

i. decline to sign a document from within your signing session, and on the subsequent page, select the check-box indicating you wish to withdraw your consent, or you may;

ii. send us an email to vincent.hughes@veristat.com and in the body of such request you must state your email, full name, mailing address, and telephone number. We do not need any other information from you to withdraw consent.. The consequences of your withdrawing consent for online documents will be that transactions may take a longer time to process..

Required hardware and software

The minimum system requirements for using the DocuSign system may change over time. The current system requirements are found here: https://support.docusign.com/guides/signer-guide-signing-system-requirements.

Acknowledging your access and consent to receive and sign documents electronically

To confirm to us that you can access this information electronically, which will be similar to other electronic notices and disclosures that we will provide to you, please confirm that you have read this ERSD, and (i) that you are able to print on paper or electronically save this ERSD for your future reference and access; or (ii) that you are able to email this ERSD to an email address where you will be able to print on paper or save it for your future reference and access. Further, if you consent to receiving notices and disclosures exclusively in electronic format as described herein, then select the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

By selecting the check-box next to 'I agree to use electronic records and signatures', you confirm that:

- You can access and read this Electronic Record and Signature Disclosure; and
- You can print on paper this Electronic Record and Signature Disclosure, or save or send this Electronic Record and Disclosure to a location where you can print it, for future reference and access; and
- Until or unless you notify Veristat as described above, you consent to receive exclusively through electronic means all notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you by Veristat during the course of your relationship with Veristat.